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Low-Concentration $PM_{2.5}$ and Mortality: Estimating Acute and Chronic Effects in a Population-Based Study

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Short title: Low-concentration $PM_{2.5}$ and mortality

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Abstract

Background: Both short- and long-term exposures to fine particulate matter ($PM_{2.5}$) are associated with mortality. However, whether the associations exist below the new EPA standards (12 $\mu g/m^3$ of annual average $PM_{2.5}$, 35 $\mu g/m^3$ daily) is unclear. In addition, it is not clear whether results of previous time series studies (fit in larger cities) and cohort studies (fit in convenience samples) are generalizable to the general population.

Objectives: To estimate the effects of low-concentration $PM_{2.5}$ on mortality.

Methods: High resolution (1 × 1 km) daily $PM_{2.5}$ predictions, derived from satellite aerosol optical depth retrievals, were employed. Poisson regressions were applied to the Medicare population (age>=65) in New England to simultaneously estimate the acute and chronic effects, with mutual adjustment for short- and long-term exposure, as well as area-based confounders. Models were also restricted to annual concentrations below 10 $\mu g/m^3$ or daily concentrations below 30 $\mu g/m^3$.

Results: $PM_{2.5}$ was associated with increased mortality. In the cohort, 2.14% (95% CI: 1.38, 2.89%) and 7.52% (95% CI: 1.95, 13.40%) increases were estimated for each 10 $\mu g/m^3$ increase in short- (2 day) and long-term (1 year) exposures, respectively. The associations still held for analyses restricted to low-concentration $PM_{2.5}$ exposures. The corresponding estimates were 2.14% (95% CI: 1.34, 2.95%) and 9.28% (95% CI: 0.76, 18.52%). Penalized spline models of long-term exposure indicated a higher slope for mortality in association with exposures above versus below 6 $\mu g/m^3$. In contrast, the association between short-term exposure and mortality appeared to be linear across the entire exposure distribution.

Conclusions: Using a mutually adjusted model, we estimated significant acute and chronic effects of $PM_{2.5}$ exposures below current EPA standards. These findings suggest that improving air quality below current standards may benefit public health.

Introduction

Many studies have found association between fine particulate matter (PM with aerodynamic diameter ≤ 2.5 μm [$PM_{2.5}$]) and increased mortality (Dockery et al. 1993; Schwartz 1994; Pope III et al. 2002; Franklin et al. 2007; Zanobetti and Schwartz 2009). Biological evidence has been established for plausible mechanisms between $PM_{2.5}$ and mortality, such as increased risk of ventricular arrhythmia and thrombotic processes, increased system inflammation and oxidative stress, increased blood pressure, decreased plaque stability, and lower lung function, among others (Downs et al. 2007; Gauderman et al. 2004; Suwa et al. 2002; Brook et al. 2009; Gurgueira et al. 2002; Yue et al. 2007). Based on evidence from epidemiological and toxicological studies (Chen and Nadziejko 2005; Furuyama et al. 2006; Ohtoshi et al. 1998), National Ambient Air Quality Standards (NAAQS) were implemented for fine particulate matter. For example, U.S. Environmental Protection Agency (EPA) revised the fine particle NAAQS in the years of 1997, 2006, and 2012, in order to protect public health (EPA 1997; EPA 2006; EPA 2013). Further changes in the standards require additional studies to elucidate whether health effects occur at levels below current annual and daily EPA NAAQS of 12 and 35 $\mu g/m^3$, respectively. The Clean Air Act requires EPA to review national air quality standards every five years to determine whether they should be retained or revised (United States Code Title 42, Chapter 85), thus whether the relationship continues below the current standards is of great interest and importance.

Previous studies have generally focused on either long-term (Hart et al. 2011; Puett et al. 2009; Schwartz 2000; Jerrett et al. 2005) or short-term (Schwartz and Dockery 1992; Katsouyanni et al. 1997; Dominici et al. 2006; Samoli et al. 2008) exposures across the entire range of $PM_{2.5}$ concentration. In the case of time series analyses of short-term exposures, the

need to ensure the relevance of the monitoring data and sufficient population for power has limited analyses to larger cities, and hence exurbs, smaller cities, and rural areas are not generally represented in the literature. This may compromise the generalizability of the results. In addition, there is spatial variability in $PM_{2.5}$ concentrations within cities that time series studies generally have not taken into account, introducing exposure measurement error (Lepeule et al. 2012; Laden et al. 2006).

Chronic effects studies began using comparisons across cities of mortality experiences of a cohort living in various communities and the monitored air pollutant concentrations in those communities (Dockery et al. 1993; Pope et al. 1995). Again, these suffered from exposure error due to failure to capture within city spatial variability in exposure. Since the geographic exposure gradient is the exposure contrast in these studies, the failure to capture within city contrasts leads to classical measurement error, with expected downward bias. Studies with e.g., land use regression estimates of exposure have generally reported larger effect sizes (Puett et al. 2009; Miller et al. 2007). Previous cohort studies have not controlled for the acute effects of particles when estimating chronic effects, raising the question of whether there are independent chronic effects that represent more than the cumulative effects of acute responses.

In general, existing study cohorts are not representative of the population. For example, the American Cancer Society (ACS) cohort has higher education than the US population as a whole (Stellman and Garfinkel 1986). Hence, there have been few population-based cohort studies conducted until recently (Kloog et al. 2013).

Several time series studies examined the concentration-response relationship between $PM_{2.5}$ and mortality below concentrations of 100 $\mu g/m^3$. They generally report linear concentration-

response (Samoli et al. 2008; Schwartz and Zanobetti 2000). However, there have been few studies focusing on exposures below the current daily EPA standard of 35 $\mu g/m^3$.

More studies have examined the shape of the concentration-response curve for long-term exposure versus short-term exposure, but they have mostly not covered population based cohorts, or included very low exposures (Schwartz et al. 2008; Crouse et al. 2012).

We recently presented a new hybrid method of assessing temporally- and spatially-resolved $PM_{2.5}$ exposure for epidemiological studies by incorporating 1 × 1 km resolution satellite-retrieved Aerosol optical Depth (AOD) measurements, combined with traditional land use terms, meteorological variables and their interactions (Kloog et al. 2014a). This approach allows for predicting daily $PM_{2.5}$ concentrations at a 1 × 1 km spatial resolution throughout the New England area. We also validated our models performance in rural areas: Ten-fold cross-validation of our model in rural areas (using the IMPROVE stations) resulted in a CV R^2 of 0.92. Further details have been published (Kloog et al. 2014a).

The present study aims to simultaneously estimate acute and chronic health effects of $PM_{2.5,}$ in a population-based Medicare cohort (age $\geq$ 65) encompassing the New England region. It uses high spatial resolution exposure estimates based on satellite measurements that are available across the region and not just in limited locations. To make this study relevant to future assessments of current EPA standards, we repeated the analysis after restricting the data to long-term exposures (365-day moving average) below 10 $\mu g/m^3$, and repeated the time series analysis of short-term exposures after restricting data to two day average exposures below 30 $\mu g/m^3$.

Methods

Study domain: The spatial domain of our study included the New England area, comprising the states of Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont (Figure 1A).

Exposure data: Novel models for predicting daily $PM_{2.5}$ were previously reported incorporating AOD and land use data for the New England region (Kloog et al. 2011). Previous papers have shown that using actual physical measurements in our prediction models improves predictive accuracy over comparable land use or spatial smoothing models (Kloog et al. 2011). With AOD retrieved by Multi-Angle Implementation of Atmospheric Correction (MAIAC) algorithm, a similar approach was applied for estimating daily $PM_{2.5}$ exposures in New England at a spatial resolution of 1 × 1 km (Kloog et al. 2014a). In this study, the same $PM_{2.5}$ exposure predictions were employed.

In brief, we calibrated the AOD-$PM_{2.5}$ relationship on *each day* during the study period (2003-2008) using data from grid cells with both ground $PM_{2.5}$ monitors and AOD measurements (stage 1), and used inverse probability weighting to address selection bias due to non-random missingness patterns in the AOD measurements. We then used the AOD-$PM_{2.5}$ relationship to predict $PM_{2.5}$ concentrations for grid cells that lacked monitors but had available AOD measurement data (stage 2). Finally, we used a generalized additive mixed model (GAMM) with spatial smoothing and a random intercept for each 1 × 1 km grid cell to impute data for grid cell/days when AOD measurements were not available (stage 3). The performance of the estimated $PM_{2.5}$ was validated by ten-fold cross-validation. High out-of-sample R^2 (R^2=0.89, year to year variation 0.88 - 0.90 for the years 2003-2008) was found for days with available AOD data. Excellent performance held *even in cells/days with no available AOD* (R^2=0.89, year

to year variation 0.87 - 0.91 for the years 2003-2008). The 1 km model has better spatial (0.87) and temporal (0.87) out of sample R^2 than the previous 10 km model (0.78 and 0.84 respectively). Details of the $PM_{2.5}$ prediction models are found in Kloog et al (Kloog et al. 2014a).

Figure 1A shows an example of mean $PM_{2.5}$ concentrations in 2004 at a 1 × 1 km spatial resolution across New England. By averaging our estimated daily exposures at each location we generated long-term exposures.

Figure 1B (a subset of the study area) shows that spatial variability exists even for daily data, and is not identical to the long-term pattern shown in Figure 1A. That is, there is space-time variation in the $PM_{2.5}$ exposure captured in this analysis, but not in previous time series analyses.

Because the deaths were coded at the ZIP code level, both long- and short-term predictions were matched to ZIP codes by linking the ZIP code centroid to nearest $PM_{2.5}$ grid, using ArcGIS (ESRI, Redlines, CA) and SAS (SAS Institute, Cary, NC).

Traditionally, studies of the acute air pollution effects have controlled for temperature using values taken from the nearest airport. This approach is not feasible for the entire region, since too many residences are distant from airports. In addition, there is spatio-temporal variation in temperature as well. We have used similar models of satellite data to fit models for temperature in New England on a 1 km temperature data estimated from surface temperature measured by satellites (Kloog et al. 2014b). To our knowledge, such fine control for temperature has not previously been used in air pollution epidemiology.

Mortality data: Individual mortality records were obtained from the US Medicare program for all residents aged 65 and older for all available years during 2003-2008 (CMS). The MEDICARE cohort was used because of availability of ZIP code of residence data, whereas

National Center for Health Statistics mortality data is only available on a county level. Additionally, prior studies found that elderly people are more susceptible to the effects of particulate matter (Pope 3rd 2000). The Medicare beneficiary denominator file from the Centers for Medicare and Medicaid services (CMS) lists all beneficiaries enrolled in the Medicare fee-for-service (FFS), and contains information on beneficiaries' eligibility and enrollment in Medicare, and the date of death (CMS). The Medicare Provider Analysis and Review (MEDPAR) inpatient data includes information on age, gender, race, ZIP code of residence, and one record for each hospital admission (CMS).

Daily mortality was first aggregated by ZIP code, and then matched with the corresponding $PM_{2.5}$ exposure. We summarized the mortality data by ZIP code and day because that is the finest resolution of address we can obtain. Since the mortality datasets did not include changes of residence, we had to assume that the subjects lived at their current address over the study period.

Covariates: We used daily 1 km temperature data estimated from surface temperature measured by satellites (Kloog et al. 2014b). All socio-economic variables were obtained through the U.S. Census Bureau 2000 Census Summary File 3, which includes social, economic, and housing characteristics [United States Census Bureau (USCB) 2000]. ZIP code tabulation area level socio-economic variables, including race, education, and median household income, were used. In addition, county-level percent of people who currently smoke every day from the CDC Behavioral Risk Factor Surveillance survey for the entire country was adjusted as well (CDC 2013). Dummy variables were used to control for day of the week.

Statistical Models: Conventionally, the acute effects of air pollution are estimated by Poisson log-linear models and the chronic effects are estimated by Cox proportional hazard models (Laden et al. 2006; Kloog et al. 2013). Laird and Oliver pointed out the equivalence of

the likelihood of a proportional hazard model with piecewise constant hazard for each year of follow-up and a Poisson regression with a dummy variable for each year of follow-up (Laird and Olivier 1981). We have taken advantage of this to generalize from dummy variables for each year to a spline of time to represent the baseline hazard, and to aggregate subjects into counts per person time at risk and obtained a mixed Poisson regression model (Kloog et al. 2012). This approach allows one to model the rate of death as a function of both *long*- and *short-term* exposures simultaneously. By doing so, we achieve the equivalence of a separate time series analysis for each ZIP code, greatly reducing the exposure error in that part of the model, while simultaneously conducting a survival analysis on the participants, and also are able to estimate the independent effects of both exposures.

Most time series studies have reported stronger associations with acute exposures when exposures are defined as mean $PM_{2.5}$ on the day of death and the previous day (lag01), compared with mean $PM_{2.5}$ on the current day only, or for exposures with longer lags (Schwartz et al. 1996; Schwartz 2004). We used the lag01 average for our main analysis, but performed a sensitivity analysis on that choice. Long-term exposure was calculated as the 365-day moving average ending on date of death so that our results were comparable with previous studies (Lepeule et al. 2012; Schwartz et al. 2008). Short-term exposure was defined as the *difference* between the 2-day average and the long-term average, ensuring the acute and chronic effects are independent. We subtracted the long-term average from the short-term to avoid collinearity issues, and to ensure that differences between ZIP codes in $PM_{2.5}$ at a given time do not contribute to the short-term effect estimate. Hence, the short-term effect cannot be confounded by variables that differ across ZIP codes.

Specifically, we fit a Poisson survival analysis with a logarithmic link function and a log (population) offset term and modeled the expected daily death counts (μ_{it}) in the ith ZIP code on the tth day as follows:

$$\log(\mu_{it}) = \lambda_i + \beta_1 PM_{it} + \beta_2 \Delta PM_{it} + \lambda(t) + \text{temporal covariates} + \text{spatial covariates} + \text{offset} \quad [1]$$

Where λ_i is a random intercept for each ZIP code, PM_{it} is the 365-day moving average ending on day t in ZIP code i, ΔPM_{it} is the deviation of the 2-day average from its long-term average (PM_{it}) in ZIP code i, $\lambda(t)$ is a smooth function of time, temporal covariates are temperature and day of the week, spatial covariates are socio-economic factors defined at ZIP code level (percent of people without high school education, percent of white people, median household income) and smoking data at the county level. Additionally, a Quasipoisson model was used to control for possible overdispersion (Ver Hoef and Boveng 2007).

$\lambda(t)$ was estimated with a natural cubic spline with 5 degrees of freedom (df) per year, to control for time and season trends. The specific temporal and spatial covariates we used were: a natural cubic spline for temperature with 3 df in total; a categorical variable for day of the week; linear variables for percent of people without high school education, percent of white people, median household income, and percent of people who currently smoke every day.

The number of deaths per ZIP code area over the study period (2003-2008) averaged 319 with a standard deviation of 430. Since the outcome is counts, we cannot adjust for age and sex as in a Cox model. Instead we adjust for variables that vary by ZIP code. The analyses were also repeated without mutual adjustment for short- and long-term $PM_{2.5}$.

We modeled the association between all-cause mortality and $PM_{2.5}$ at low doses in which the person-time at risk in each year of follow-up in each ZIP code was used as the offsets. We also

conducted effect modification by population size, by choosing the median (4,628) of ZIP code level total population as the cutoff between urban and rural areas.

Estimating the effects of low-level $PM_{2.5}$: For full cohort analyses with 10,938,852 person-years of follow-up, all observed deaths were used. To estimate effects at low levels of exposure we carried out restricted analyses; we conducted one analysis restricted to annual exposures below 10 $\mu g/m^3$, below the current annual $PM_{2.5}$ NAAQS of 12 $\mu g/m^3$; and another restricted to observations with short-term exposure below 30 $\mu g/m^3$, below the current daily $PM_{2.5}$ NAAQS of 35 $\mu g/m^3$. After these exclusions, the chronic analyses were restricted to 268,050 deaths out of 551,024 deaths in total, and the acute analyses to 422,637 deaths.

Assessing the dose-response relationship: For both the acute and chronic analyses, we fit penalized regression splines in the restricted analyses to estimate the shape of the dose-response below current EPA standards. The degrees of freedom of the penalized splines for $PM_{2.5}$ was estimated by generalized cross validation (GCV).

Results

Table 1 presents a summary of the predicted exposures for both the short-and long-term $PM_{2.5}$ exposure across all grid cells in the study area.

Table 2 presents the estimated percent change in all-cause mortality with 95% CIs for a 10 $\mu g/m^3$ increase for both short- and long-term $PM_{2.5}$ in the restricted and full cohort. For the restricted population, we found an estimated 9.28% increase in mortality (95% CI: 0.76, 18.52%) for every 10 $\mu g/m^3$ increase in long-term $PM_{2.5}$ exposure. For every 10 $\mu g/m^3$ increase in short-term $PM_{2.5}$ exposure, a 2.14% increase in mortality (95% CI: 1.34, 2.95%) was observed. For long-term exposure, the effect estimates were smaller when higher pollution days were included

(7.52%; 95% CI: 1.95, 13.40%), suggesting larger slopes between low-concentration long-term $PM_{2.5}$ and mortality.

Without mutual adjustment, lower estimates were found for both acute and chronic effects, compared to those with mutual adjustment. In full cohort analyses, 2.08% (95% CI: 1.32, 2.84%) and 6.46% (95% CI: 0.93, 12.30%) increase in mortality was found for each 10 $\mu g/m^3$ increase in short- and long-term $PM_{2.5}$, respectively. In restricted analyses, the corresponding effect estimates were 2.07% (95% CI: 1.27, 2.89%) and 7.16% (95% CI: -1.23, 16.27%), respectively.

Our results were robust to the choice of lag period for acute exposure. We analyzed other averaging periods (Figure 2): for example, lag0 (day of death exposure) and lag04 (a moving average of day of death exposure and previous 4-day exposure). For the acute effects, we found a significant but smaller association for lag0 $PM_{2.5}$ (1.71%; 95% CI: 1.09, 2.34%) or lag04 $PM_{2.5}$ (1.76%; 95% CI: 0.72, 2.81%) compared to lag01 analysis. The lag period used for short-term exposure did not affect estimates of chronic effects. For example, estimated increases in mortality with a 10 $\mu g/m^3$ increase in long-term $PM_{2.5}$ were 7.35% (95% CI: 1.79, 13.21%) and 7.25% (95% CI: 1.69, 13.12%) when short-term $PM_{2.5}$ was classified using lag0 or lag04, respectively.

We also examined effect modification by population size. In the full cohort, a significant interaction for chronic effects was found ($p < 0.01$), with a higher effect of 12.56% (95% CI: 5.71, 19.85%) in urban areas compared to 3.21% (95% CI: -2.92, 9.72%) in rural areas. Such a significant interaction, however, was not observed in the restricted analysis ($p = 0.16$). Estimates were 14.27% (95% CI: 3.19, 26.53%) and 5.48% (95% CI: -4.21, 16.16%) in urban and rural areas, respectively. For the short-term exposure, population size did not modify the acute effects neither in full cohort nor in restricted analyses ($p = 0.74$ and 0.46, respectively).

In our penalized spline model for long-term exposure below the cutoff of 10 μg/m^3 (Figure 3a), we found a non-linear relationship between long-term $PM_{2.5}$ and mortality. The association was linear with evidence of a lower slope below 6 μg/m^3. However a large confidence interval was observed; hence we could not be confident whether the slope of the dose-response curve for long-term exposures below 6 μg/m^3 changed. When examining the shape of the dose-response for chronic effects, both a linear term for short-term exposure (*the difference*) and a penalized spline for long-term average exposure were included in the model, resulting in a penalized spline with a df of 1.71. In contrast, we only included the 2-day average in the penalized spline model of acute effects, to provide a more interpretable dose-response relationship (Figure 3b). Results of this analysis indicated a linear association across the exposure distribution, but we could not be certain about the shape of slope for acute effects below 3 μg/m^3.

Discussion

Applying the predicted daily $PM_{2.5}$ with 1 km spatial resolution from our novel hybrid models, we observed that both short- and long-term $PM_{2.5}$ exposure were significantly associated with all-cause mortality among residents aged 65 and above in New England, even when restricted to ZIP codes and times with annual exposures below 10 μg/m^3 or with daily exposure below 30 μg/m^3. Hence the association of particle exposure with mortality exists for concentrations below current US, WHO (10 μg/m^3 of annual average $PM_{2.5}$, 25 μg/m^3 daily) or EU (25 μg/m^3 of annual average $PM_{2.5}$) standards (WHO; EU). Notably, this analysis includes all areas in New England and all Medicare enrollees aged 65 and above, and provides chronic effect estimates that are independent of acute effects. Based on a penalized spline model, the positive dose-response relationship between chronic exposure and mortality appears to be linear for $PM_{2.5}$ concentrations down to 6 μg/m^3, with a positive (though weaker and less precise) dose-

response slope continuing below this level. This lack of power is likely due to the small population exposed in the areas with annual $PM_{2.5}$ below 6 $\mu g/m^3$, which were quite rural.

For the acute effect, we found a 2.14% (95% CI: 1.38 to 2.89%) increase in all-cause mortality per 10 $\mu g/m^3$ increment in $PM_{2.5}$ for the full cohort of our study, which is higher than the effect size of most studies using city averages from monitors. For instance, in a US national study by Zanobetti and Schwartz (Zanobetti and Schwartz 2009), the effect size was found to be 0.98% (95% CI: 0.75, 1.22%). Similar results have also been found in a review study, where researchers have demonstrated the overall summary estimate was 1.04% (95% CI: 0.52, 1.56%) per 10 $\mu g/m^3$ increment in $PM_{2.5}$ (Atkinson et al. 2014). Most previous studies had exposure data with lower spatial resolution (citywide average, not ZIP code), which introduces exposure measurement error and likely results in downward bias in estimates; these results (for the acute effect) are consistent with such a phenomena. Our restricted study estimated a 2.14% (95% CI: 1.34, 2.95%) increase in all-cause mortality per 10 $\mu g/m^3$ increment in $PM_{2.5}$, close to the effect size of the full cohort study, possibly because the sample size of the restricted study for acute effect is close to that of the full cohort. That is, the EPA daily standard (35 $\mu g/m^3$) was almost never exceeded in this study. In addition, lower effect estimates for short-term exposure were observed with mutual adjustment for both full cohort and restricted analyses. This finding has important implications for the interpretation of previous studies without such mutual adjustment.

For the chronic effect, the effect estimate in our full cohort study is consistent with previous studies with comparable sample sizes (Lepeule et al. 2012; Laden et al. 2006; Hoek et al. 2013). For example, ACS study comprised of 500,000 adults from 51 US cities, reported a 6% (95% CI: 2, 11%) increase in all-cause mortality for 10 $\mu g/m^3$ increment in $PM_{2.5}$ (Pope III et al. 2002). A study of 13.2 million elderly Medicare recipients across the east USA found a 6.8% (95% CI:

4.9, 8.7%) increase in all-cause mortality for 10 μg/m^3 increment in $PM_{2.5}$ (Zeger et al. 2008). When we restricted our analysis to annual concentrations below 10 μg/m^3, a larger slope of 9.28% (95% CI: 0.76, 18.52%) increase per 10 μg/m^3 was observed. Our findings suggest a steeper slope at low concentrations among those aged 65 years and older. This may also reflect particle composition. The sources and composition of the particles may differ on lower pollution days from that seen on high pollution days, which are probably more impacted by secondary aerosols. Compared to the full cohort, the effect estimate of the restricted analysis was closer to the estimates in the published literature reporting higher slopes, such as the ESCAPE study, the Six City study and Women's Health Initiative study (Beelen et al. 2014; Puett et al. 2008). Lower effect estimates were also observed for chronic effect without mutual adjustment.

To the best of our knowledge, this study is the first of its kind restricting the exposure and exploring the dose-response relationship between $PM_{2.5}$ and mortality below the current EPA standards (12 μg/m^3 of annual average $PM_{2.5}$, 35 μg/m^3 daily). Moreover, the use of the MEDICARE cohort means we are studying the entire population of Medicare enrollees over 65, and not a convenience sample. In addition, temperature was also controlled on the 1 × 1 km fine geographic scale. The acute and chronic effects for analyses restricted to low exposure of $PM_{2.5}$ are similar or even higher compared to those of the full cohort analyses. These results indicate that the adverse health effects of $PM_{2.5}$ are at least retained, if not strengthened, at low levels of exposure. However, the findings from the penalized spline model do not support a stronger association at the lowest range of $PM_{2.5}$ concentrations. This finding provides epidemiological evidence for the reevaluation of EPA guidelines and standards, though more evidence are needed to confirm the association below 6 μg/m^3.

The Poisson survival analysis applied in this study provides new opportunities in assessing acute and chronic effects simultaneously. As shown in our analysis, the chronic effect estimate was much larger than the acute effect estimate, after controlling for the acute estimate, indicating there was chronic effect of $PM_{2.5,}$ which cannot be solely explained by the short-term exposure.

Another key component of this study is that the application of high spatial- (1 × 1 km) and temporal- (daily) resolution of $PM_{2.5}$ concentrations to some extents reduced exposure error. The out-of-sample R^2 is higher than that for the predictions with 10 × 10 km spatial resolution.

A potential limitation is the limited availability of individual level confounders, such as smoking status, which could bias the health effect estimates. We were able to control for ZIP code level education, median income, race and county level smoking data. However, a study by Brochu et al. reported that census tract level socioeconomic indicators were uncorrelated with $PM_{2.5}$ on the subregional and local scale, providing some assurance that confounding by SES may not be much of an issue (Brochu et al. 2011). These results suggest that those variables may not confound the association, but the inability to control for them remains an issue. Another limitation is that we did not examine other pollutants such as O_3 or NO_2 due to lack of data at the same spatial level as $PM_{2.5}$.

In conclusion, the acute and chronic effects of low-concentration $PM_{2.5}$ were examined for Medicare population using a comprehensive exposure dataset from a satellite-based prediction model. Our findings show that both short- and long-term exposure to $PM_{2.5}$ were associated with all-cause mortality, even for exposure levels not exceeding the newly revised EPA standards, suggesting that adverse health effects occur at low levels of fine particles. The policy implication is that improving the air quality below the current EPA standards can still yield health benefit.

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Table 1. Descriptive Statistics for $PM_{2.5}$ exposure and temperature in New England, 2003-2008.

Covariate	Mean	SD	Min	Median	Max	Range	Q1	Q3	IQR
Lag01 $PM_{2.5}$ ($\mu g/m^3$)	8.21	5.10	0.00	7.10	53.98	53.98	4.60	10.65	6.05
1-year $PM_{2.5}$ ($\mu g/m^3$)	8.12	2.28	0.08	8.15	20.22	20.14	6.22	10.00	3.78
Temperature (˚C)	9.24	6.50	-36.79	9.81	41.51	78.30	4.90	14.39	9.49

Table 2. Percent increase in mortality (95% CI) for a 10 μg/m^3 increase for both short-term and long-term $PM_{2.5}$.

$PM_{2.5}$ exposure	**Model**	**Percent increase**	***p*-value**
With mutual adjustment			
Short term $PM_{2.5}$	Low daily exposure[a]	2.14 ± 0.81	<.001
	Full cohort	2.14 ± 0.75	<.001
Long term $PM_{2.5}$	Low chronic exposure[b]	9.28 ± 8.88	0.032
	Full cohort	7.52 ± 5.73	0.007
Without mutual adjustment			
Short term $PM_{2.5}$	Low daily exposure[a]	2.07 ± 0.80	<.001
	Full cohort	2.08 ± 0.76	<.001
Long term $PM_{2.5}$	Low chronic exposure[b]	7.16 ± 8.75	0.109
	Full cohort	6.46 ± 5.69	0.026

[a]The analysis was restricted only to person time with daily $PM_{2.5}$ less than 30 μg/m^3 (422,637 deaths).

[b]The analysis was restricted only to person time with chronic $PM_{2.5}$ less than 10 μg/m^3 (268,050 deaths). The full cohort analysis had 551,024 deaths.

Figure Legends

Figure 1. A. Mean $PM_{2.5}$ concentrations in 2004 at a high resolution (1 × 1 km) across New England predicted by the AOD models. **B.** Predicted $PM_{2.5}$ concentrations at a 1 × 1 km grid for November 15, 2003.

Figure 2. Percent change in mortality per 10 μg/m^3 increase in short-term $PM_{2.5}$ with different lags with mutual adjustment. Error bars indicate the 95% CIs.

Figure 3. The dose-response relationship between long-term $PM_{2.5}$ and mortality at low doses with mutual adjustment (a) and the dose-response relationship between short-term $PM_{2.5}$ and mortality at low doses without mutual adjustment (b). Shaded areas indicate the 95% CIs.

Figure 1A.

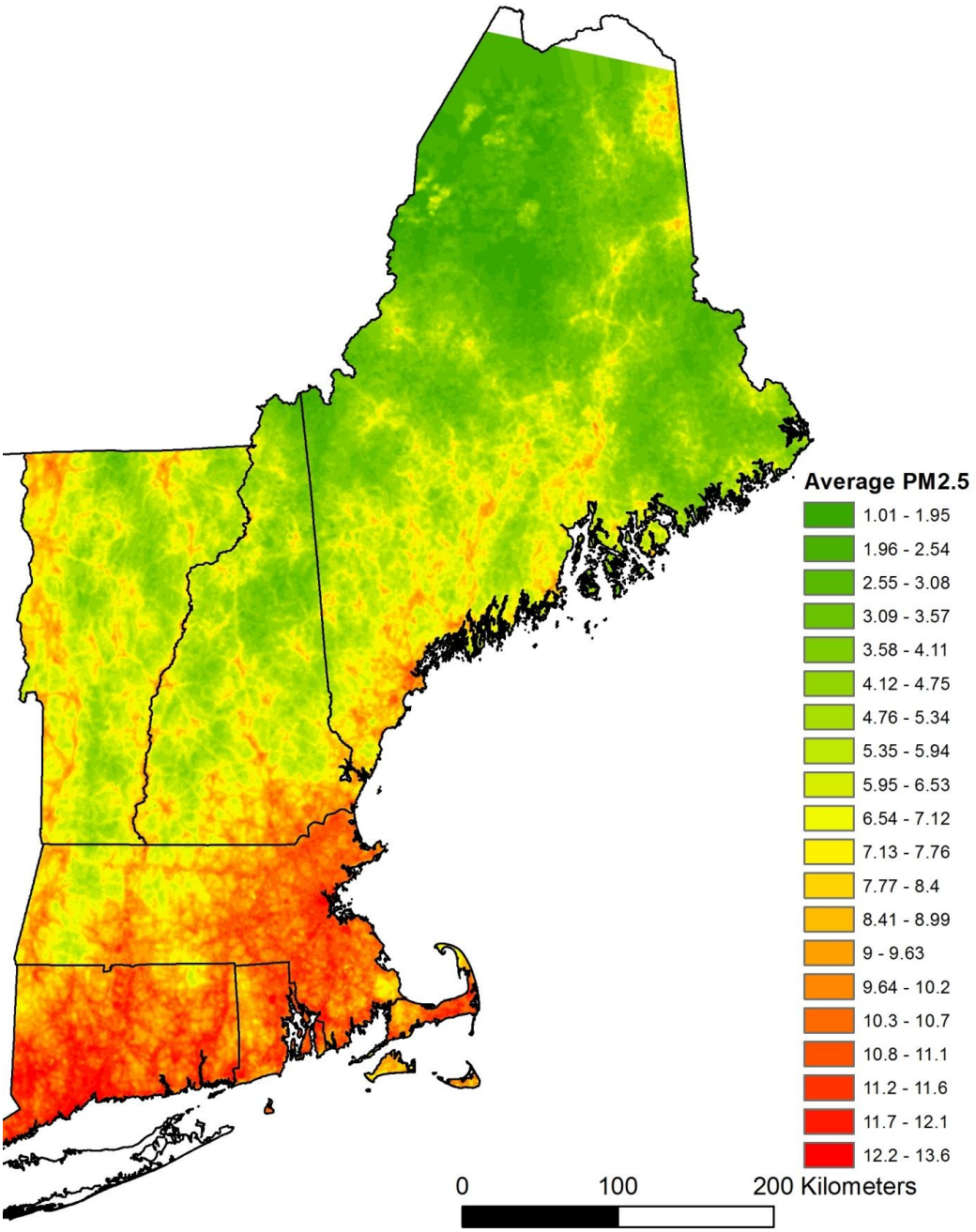

Average PM2.5
1.01 - 1.95
1.96 - 2.54
2.55 - 3.08
3.09 - 3.57
3.58 - 4.11
4.12 - 4.75
4.76 - 5.34
5.35 - 5.94
5.95 - 6.53
6.54 - 7.12
7.13 - 7.76
7.77 - 8.4
8.41 - 8.99
9 - 9.63
9.64 - 10.2
10.3 - 10.7
10.8 - 11.1
11.2 - 11.6
11.7 - 12.1
12.2 - 13.6
0
100
200 Kilometers

Figure 1B.

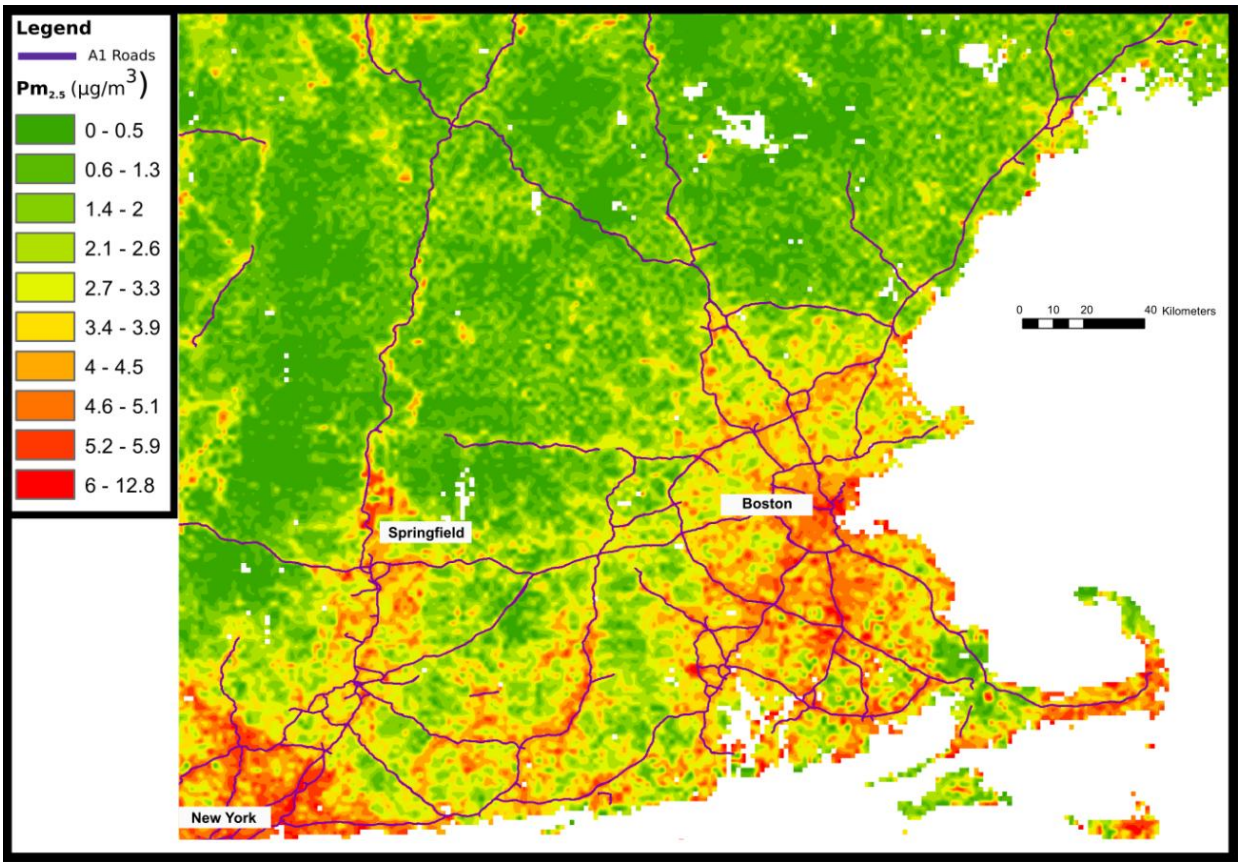

Legend
A1 Roads
Pm2.5 (µg/m3)
0 - 0.5
0.6 - 1.3
1.4 - 2
2.1 - 2.6
2.7 - 3.3
3.4 - 3.9
4 - 4.5
4.6 - 5.1
5.2 - 5.9
6 - 12.8
0 10 20 40 Kilometers
Springfield
Boston
New York

Figure 2.

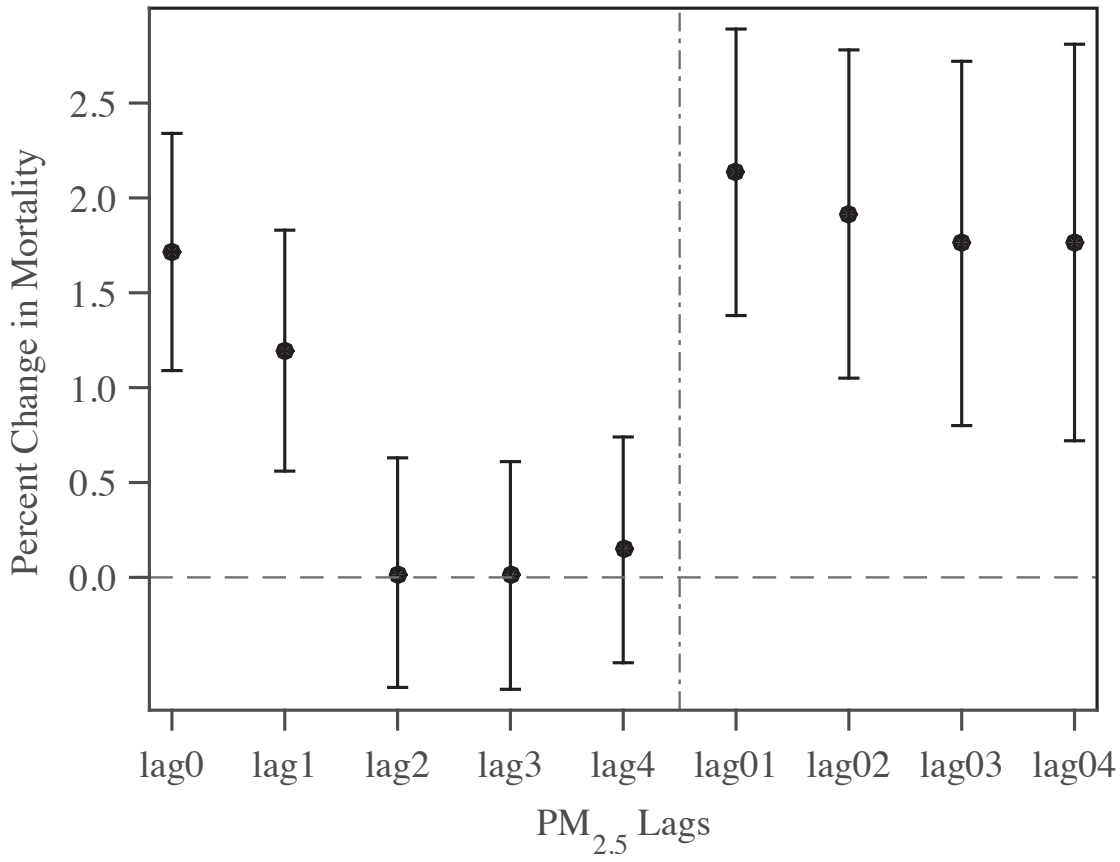
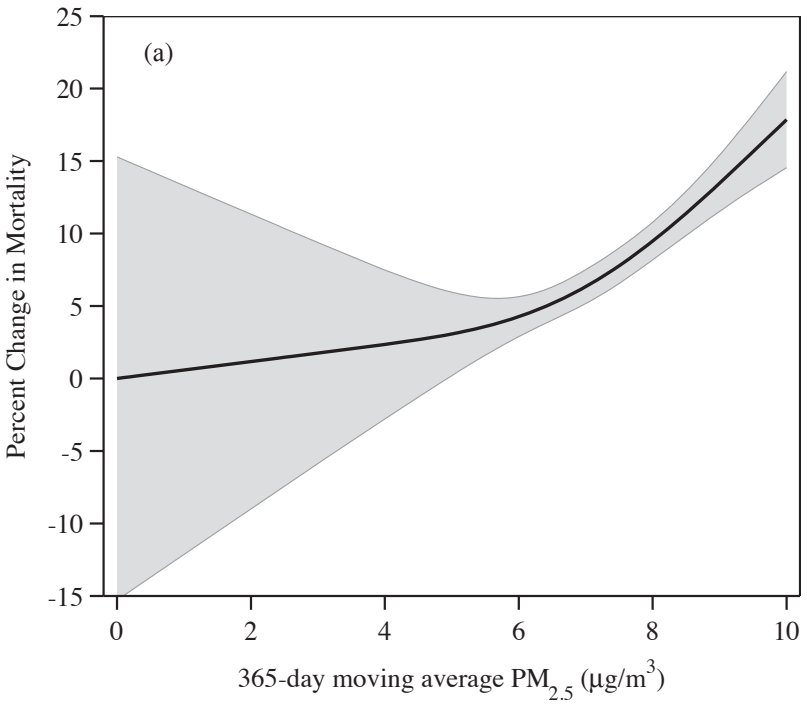
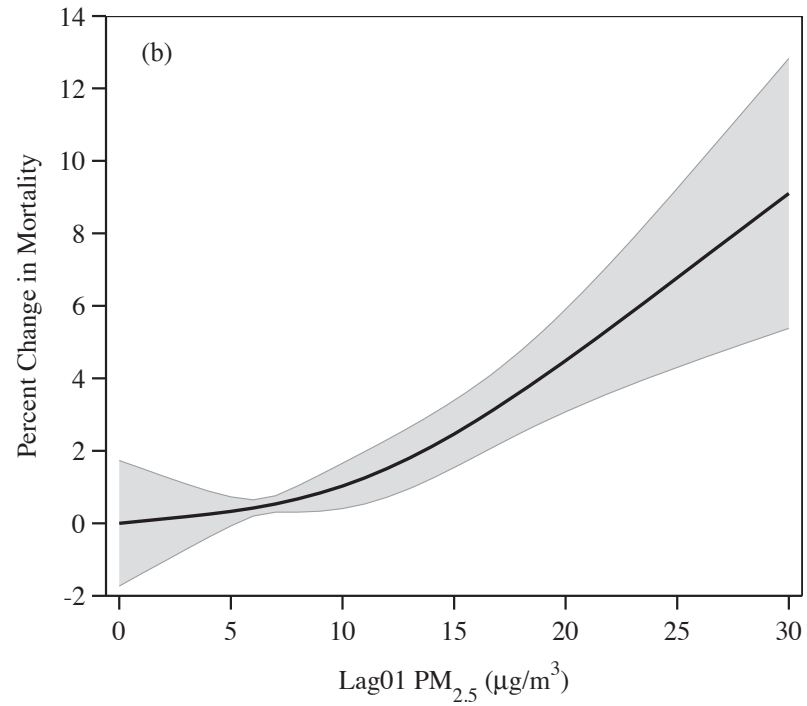

Percent Change in Mortality
2.5
2.0
1.5
1.0
0.5
0.0
lag0
lag1
lag2
lag3
lag4
lag01
lag02
lag03
lag04
PM2.5 Lags

Figure 3.


(a)
Percent Change in Mortality
25
20
15
10
5
0
-5
-10
-15
0
2
4
6
8
10
365-day moving average $PM_{2.5}$ ($\mu g/m^3$)


(b)
Percent Change in Mortality
14
12
10
8
6
4
2
0
-2
0
5
10
15
20
25
30
Lag01 $PM_{2.5}$ ($\mu g/m^3$)